THE SYNTHESIS OF SOME NEW DERIVATIVES OF CINNAMIC ACID AND O-OXYDIPHENYL

by

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Introduction.

The purpose of this research was to build up derivatives of cinnamic acid (especially of its benzyl ester) and of o-oxydiphenyl for further use in bacteriological and biological work in connection with the prevention or cure of tuberculosis. Much work has been done on chemico-therapeutic treatment of tuberculosis, and many simple compounds have been used with varying degrees of success (outlined below). It was held by certain physicians of Vancouver that if these various simple substances could be united and yet retain their individual effect on the disease, a more efficient method of treatment could be devised. We have worked solely with this end in view, since the synthesis of a new compound for no other reason than that it is new is now generally considered a waste of time and money, rather than an original contribution to progress.

A detailed list of the simpler compounds already tried, together with the source of information, follows.

The "British Medical Journal," Dec. 26, 1908, p. 1893, and the "Lancet," vol. 1, 1909, p. 413 describe the use of sodium cinnamate. Calmette, in his text "Tuberculous Infection and Tuberculosis in Man and Animals," p. 665, states that benzyl alcohol has a solvent action on the tough

linings of the bacilli. Benzyl cinnamate is being used today by injecting its solution in olive oil (H. Gainsborough, Lancet, May 5, 1928, "Benzyl Cinnamic Ester in Tuberculosis."), Dr. Crile (Practitioner, 1913, "Treatment of T. B. by Nascent Iodine"), Dr. Solis Cohen (Pharmaco-Therapeutics, 1928, p. 550), and Calmette (ibid., p. 56) find nascent iodine of value. Sodium o-phenyl phenate (U. S. Dept. of Agriculture, Clip Sheet 778; Jour. Franklin Institute, July 1933) has been used with success to destroy the bacillus outside of the body. Some astonishing results have been obtained by the administration of urea, both orally and intravenously (Dr. H. Harper, Lancet, Mar. 9, 1901, and June 15, 1901, "Pure urea in the treatment of T. B.").

A. Preparation of benzyl m-iodo cinnamate.

Owing to lack of success with the method first tried (the action of benzyl chloride on the sodium salt of the acid, as outlined in the earlier paper), I tried the action of the acid chloride on benzyl alcohol. To conserve the costly iodo acid I used first cinnamyl chloride and benzyl alcohol.

6.1 parts of a warm melt of cinnamyl chloride were added slowly to 4 parts (a slight excess) of benzyl alcohol. Vigorous ebullition and intense fuming of HCl were noticed during the addition. The reaction mixture was warmed to expel HCl and ensure completion of the reaction, and subjected to vacuum distillation. A little clear oil came over up to 200°, but the larger part boiled at 237° (30 mm. pressure), in fairly close agreement with the boiling point of 225° - 235° at unspecified pressure, given by Grimaux (C.r. 67, 1049). The distillate was an oil that solidified on long standing at low temperatures. On crystallizing once from alcohol crystals were obtained which melted at 36.5°. (Melting point of benzyl cinnamate is 39° according to Grimaux).

m-iodo cinnamyl chloride.

To utilize the above method in the preparation of

benzyl m-iodo cinnamate, it was necessary first to prepare m-iodo cinnamyl chloride. Two methods were employed to do this; (1) by the action of PCl_5 (2) by the action of $SOCl_2$. The second was the one finally adopted for reasons of economy and expediency.

1. The dry acid, not crystallized, but merely precipitated from its sodium salt, was treated with a slight theoretical excess of PCl_5. On gentle warming a violent reaction ensued. After the $POCl_3$ had been distilled off on the steam bath, the main product came over at 195°- 205° (20 mm.) or 190°- 195°(16 mm.). A slight decomposition was noticed, the distillate being colored with iodine. On standing in the ice chest, crystals formed in needles radiating from various centres. The yield was between 85 - 90% of the theory.

2. With thionyl chloride it was found necessary to employ a large excess partly because of the voluminous nature of the iodo acid, partly because of the sluggish nature of the reaction. At least an equal weight of $SOCl_2$ was refluxed with the acid for several hours, until all the acid had disappeared to form a reddish brown solution and no more HCl fumes came off. If the solution was not perfectly clear, with no insoluble residue, it was found to ensure better results to filter it through asbestos. The excess $SOCl_2$ was distilled off on the steam bath and the residue subjected to vacuum distillation. Boiling point,

184° - 187° at 6 mm., 213° - 218° at 40 mm. This last is however accompanied by much decomposition, which, besides involving a loss, contaminates the distillate with iodine, which is extremely difficult to remove, even on repeated fractionations. Crystals formed in a redistilled sample at 35.3°. The product is soluble in ether, benzene, chloroform, carbon disulphide.

With the above method a yield of 93% was obtained, which makes it a better procedure than the first, since the iodo acid is comparatively expensive.

To confirm the identity of this substance I proceeded as follows: an accurately weighed sample, purified by careful fractionations, was placed in a beaker, covered with water, and decomposed by the addition of KOH. It was necessary to heat for quite a time to ensure solution. When no particles remained, the solution was acidified with HNO_3 and cooled. The white flocculent precipitate thus obtained was filtered off through asbestos, and $AgNO_3$ solution in excess was added to the filtrate, along with the washings. The AgCl so formed was then determined in the usual way, it being found necessary, however, to run blanks to determine the correction to be applied for the chlorine content of the KOH and HNO_3 used.

Results:

Wt. sample	Corrected wt. AgCl	% Cl
.3543 g.	.1741 g.	12.16 %
.3455 g.	.1709 g.	12.24 %

The calculated value for $C_6H_4I(CH)_2COCl$ is 12.13%.

This result was substantiated by an examination of the flocculent precipitate obtained on acidification in the above analysis. Recrystallized several times from dilute alcohol it gave a corrected melting point of 191.5°. This seemed high, as Gabriel and Herzberg (B. 16, 2037) give 182-3° with decomposition for m-iodo cinnamic acid, so I re-examined some iodo acid prepared from m-iodo benzaldehyde. After several crystallizations this yielded an acid with exactly the same melting point (191.5°) with very little decomposition. Gabriel's and Herzberg's results are then about 10 degrees too low, the apparent checks obtained in my first paper probably being due partly to impurities, partly to neglect of thermometer stem correction.

A consideration of the table below will indicate that the higher value is the more logical one.

Compound	M.P.	Compound	M.P.
cinnamic acid	133° C	benzoic acid	121-2° C
m-nitro " "	196-7°	m-nitro " "	140°
m-amino " "	180-1°	m-amino " "	174°
m-chlor " "	176°	m-chlor " "	153(158)°
m-brom " "	176-179°	m-brom " "	155°
m-iodo " "	181°(?) or 191.5°	m-iodo " "	188°

Preparation of the benzyl ester.

40 g. of the iodo chloride prepared as above were warmed with 15 g. $C_6H_5CH_2OH$. A vigorous evolution of HCl, accompanied by a rise in temperature was noticed. On standing, fine crystals were deposited. The reaction mixture was distilled under a vacuum, the benzyl alcohol first coming over carrying with it the iodine which had contaminated the acid chloride. At 17 mm. 45 g. (90% yield) came over between 260° - 280°. On redistillation, the major portion boiled at 265° - 275° (16 mm.). At 12 mm. a sample of this distillate boiled at 255° - 260°, and for analysis the middle portion (273° at 15-16 mm.) was taken.

The product is a pale yellow oil when distilled. On cooling, it becomes thick like honey, gradually becoming turbid. On long standing, or on cooling with ice, crystals form about several centres, like spokes in a wheel. To obtain a pure sample for analysis and melting point, it was

crystallized from 95% alcohol as follows: some of the oil was warmed with a large amount of alcohol to about 50° and stirred until no more dissolved. The clear solution was decanted from the excess oil, and the operation repeated until all the oil dissolved. On standing some time in a cool place, fine white needles separated, of melting point 50.0°. An analysis (method of Carius) gave the following results:

Sample	AgI	% I
.1968 g.	.1268 g.	34.83
.2691 g.	.1739 g.	34.93

The theoretical value for $C_6H_4I(CH)_2COOCH_2C_6H_5$ is 34.87% iodine.

The compound is very soluble in benzene, chloroform, ethyl acetate, carbon disulphide, and ether. It is only slightly soluble in cold alcohol, and insoluble in water. It is very slightly soluble in glacial acetic acid at 0°C, rather soluble at room temperature, and very soluble in the hot acid.

For quantity production of this ester I used the following modification: 40 g. of the acid were refluxed with $SOCl_2$ and the excess distilled off, the last traces being removed by warming in a vacuum. Without further purification I added to the warm mass 15-20 g. of benzyl alcohol, and proceeded as above. Yield was almost quantitative - 50 g. of

oil, not recrystallized.

B. Preparation of m-iodo benzyl cinnamate.

This was done by a method analogous to that used in preparing benzyl m-iodo cinnamate — m-iodo benzyl alcohol was allowed to react with cinnamyl chloride.

1. Preparation of m-iodo benzyl alcohol.

As I had on hand some m-iodo benzaldehyde, a direct conversion of this to m-iodo benzyl alcohol and m-iodo benzoic acid seemed the most convenient way of obtaining the former. For notes on the procedures given in the literature to this end see later. I proceeded, then, as follows:

20 g. m-iodo benzaldehyde were treated with a solution of 10 g. potassium hydroxide in 95% alcohol. The mixture became warm and solution ensued. After heating to boiling the solution was allowed to cool, and in some hours the dark liquid had become a thick paste of crystals (potassium benzoate, probably). Water was added to dissolve this by-product (or part of the alcohol was first distilled off), and the resultant clear dark brown liquid evaporated on the steam bath until most of the alcohol had been driven off. This removal was complete enough when the evolution of vapor had become very slow and the dark brown oil which collected at the bottom of the flask no longer increased. After cooling, the water solution was decanted and extracted

with ether to recover the small amount soluble in the water (small, that is, if most of the alcohol had been driven off). The dark oil was either taken up in the ether or distilled directly, depending on the amount. Treatment of the crude product with either sulphurous acid or sodium acid sulphite was found unnecessary, there being no free iodine or unconverted iodo benzaldehyde present as impurity.

The ethereal extract (or the oil) was dried with calcium chloride and distilled. At 12 mm. the major portion came over at 160°- 165°; according to Langguth (B. 38, 2063), m-iodo benzyl alcohol at 5 mm. boils at 154°.

The yield proved to be almost quantitative, being in this case just under 10 g., and in later repetitions varying from 90 - 100% of the theoretical yield.

To recover the by-product, m-iodo benzoic acid, the aqueous solution obtained as above, after being extracted with ether, was acidified with dilute sulphuric acid, and the resultant nearly white precipitate filtered off. Crystallized from acetone, the substance melted at 188°- 189°, in close agreement with the melting point of 188° given in the literature for m-iodo benzoic acid.

As the above procedure yielded such good results, most of the iodo benzyl alcohol needed was prepared so. Some, however, was made from m-nitro benzaldehyde as follows:

m-nitro benzaldehyde to m-nitro benzyl alcohol

(Becker, B. 15, 2090).

With cooling, 2 parts of m-nitro benzaldehyde were added to a solution of 1 part potassium hydroxide and 6 parts of water, and the mixture let stand overnight. (Somewhat better yields were obtained using 1.2 parts of KOH instead of 1). The product obtained by extraction with ether was used directly, without further purification, in the following reduction:

m-amino benzyl alcohol from the nitro compound

(Lutter, B. 30, 1005).

With constant cooling, 125-150 g. of mossy zinc were added gradually to a solution of 50 g. m-nitro benzyl alcohol in 200 cc. of alcohol and 325 cc. of HCl (sp. g.1.19). The mixture was left overnight, and the excess zinc then filtered off. Not desiring the pure amino compound, I attempted to vary the orthodox method as follows:

m-diazo benzyl alcohol chloride.

As the acid in the above filtrate had been practically exhausted by the excess zinc, 60-70 cc. of HCl (1.19) were first added to the sirupy filtrate; after cooling to 0°C, the amino hydrochloride solution was diazotized with 10% sodium nitrite solution, about 200 cc. being required.

Conversion of the above diazo chloride to m-iodo benzyl alcohol.

I first followed Langguth's procedure (B.38, 2063). To the above diazo solution a solution of 65 g. KI in 200cc. water was added; then, with warming, copper powder was added. (The powder paste was prepared according to Gattermann, B. 23, 1219). Vigorous ebullition ensued. At the end of the evolution of nitrogen the mixture was cooled and extracted with ether. It was found difficult to remove the fine copper powder, which may account for the poor results obtained. When vacuum distillation was attempted (after the evaporation of the ether), the result was, in several experiments, that a few grams of a clear liquid passed over at the boiling point of m-iodo benzyl alcohol, and then the residue in the flask (containing the greater part of the reaction product) foamed up, changing into a black, tarry, voluminous mass of irritating odor, with separation of iodine, which contaminated what product had already distilled over. This miscarriage seemed due to a condensation between two molecules catalysed by, perhaps, traces of copper powder. Time did not permit a close investigation, but more work is indicated (probably the substitution of another catalyst, e.g., cuprous chloride, would be sufficient, or again it might be found necessary to purify the m-amino benzyl alcohol before diazotizing).

Slightly better results were obtained by the omission of copper powder from the above procedure. The reaction was not so smooth, however, and even in this case some decomposition took place on distillation.

(Note: if the ethereal extract was a very dark red, decomposition nearly always ensued on distillation; so possibly a by-product of the reaction catalyses the undesired condensation on distillation).

It may readily be seen that the first method given above (the action of alcoholic potash on m-iodo benzaldehyde) is the most convenient and economical.

2. m-iodo benzyl cinnamate from the above.

About 13 parts (a slight excess) of a warm melt of cinnamyl chloride were poured into 16 parts of m-iodo benzyl alcohol. After a moment HCl started coming off, accompanied by a rise in temperature, until the mixture was effervescing violently. When the vigor of the reaction had somewhat abated, the flask was warmed and shaken, to obtain a more complete reaction by removal of HCl. When no more HCl was evolved, the mixture was subjected to vacuum distillation. First a yellow oil, probably the excess cinnamyl chloride, came off below 150°, then the temperature rose rapidly to 260°. The greater fraction came over fairly constantly at 262-264° at 7 mm. or 269-270° at 11-12 mm. The yield was about 75% of theoretical. As received the

distillate was a yellow oil, viscous at room temperatures and becoming almost brittle at - 20° C, without, however, crystallizing. On standing some days in the ice chest with a few seed crystals it slowly crystallized from several centres in radiating needles.

To obtain crystals for analysis, the oil was warmed to about 40° with 95% alcohol; after stirring for some time the solution was decanted through a filter and allowed to cool. Crystal formation is very sluggish, seeding with previously obtained crystals and cooling with ice and salt being necessary for best results. On rapid cooling, small rectangular prisms, of a very pale yellow, were obtained, and on slow cooling large, rectangular , almost colorless plates.

A specimen melting at 35° was analysed for iodine (method of Carius).

Sample	AgI	%I
.2374 g.	.1524 g.	34.70%
.2740 g.	.1755 g.	34.62%

The theoretical value for m-iodo benzyl cinnamate is 34.87%I.

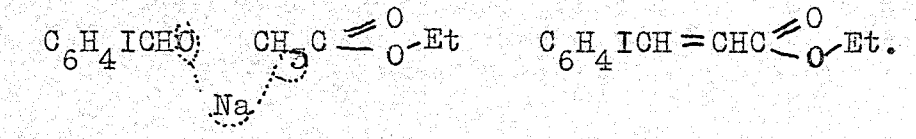
A combustion analysis gave carbon 52.5%, hydrogen 3.7%. The calculated values for m-iodo benzyl cinnamate are carbon 52.75%, hydrogen 3.6%.

From the above results it follows that there can be very little doubt as to the identity of the substance.

The action of solvents on this product is very similar to their action on benzyl m-iodo cinnamate, as was expected. It is very soluble in ether, ethyl acetate, benzene, acetone, carbon disulphide, and chloroform. It is rather insoluble in 95% alcohol or glacial acetic acid at 0°C, but very soluble in the latter at elevated temperatures, while more soluble in the former at 40°C than benzyl m-iodo cinnamate.

C. Reaction of sodium on (1) m-iodo benzaldehyde and ethyl acetate (2) benzaldehyde and benzyl acetate.

While investigating various possible methods of synthesizing benzyl m-iodo cinnamate, the work of Claisen (B. 23, 976) on condensation of benzaldehyde with ethyl acetate to ethyl cinnamate by means of sodium came to my notice. By substituting m-iodo benzaldehyde and benzyl acetate for the above a possible means of preparing benzyl m-iodo cinnamate seemed offered, although, as the work of Bacon (Am. 33, 94) showed, the substitution of the benzyl for the ethyl group affects the reactions of an ester towards sodium so markedly that there seemed little chance of working out a procedure to yield better results than that given above. However, a very convenient method for the preparation of ethyl m-iodo cinnamate seemed indicated:



I proceeded as follows:

A solution of 20 g. m-iodo benzaldehyde in about 50 cc. pure ethyl acetate was added slowly to a flask containing 2 g. of sodium wire in 50 cc. of ethyl acetate, the whole being cooled down to 0°C. After all the solution had been added, I let the reacting mixture stand until all the sodium had vanished, then added about 6 g. glacial acetic acid, mixed well and added water until all the solid sodium acetate had dissolved. The layer of esters was separated, washed with Na_2CO_3 solution, dried with $CaCl_2$, and the excess ethyl acetate distilled off. The residue was distilled in a vacuum. Boiling point, 180-190° at 16 mm. melting point 37°— the same characteristics as the ester obtained earlier by an entirely different method (Paper for the degree of Bachelor of Arts, U.B.C. 1932)[1]. To make still more certain I saponified some of the product with KOH, precipitated with H_2SO_4, and recrystallized twice from dilute alcohol. The melting point of the crystals so obtained was 191°, as found above for m-iodo cinnamic acid.

In the above procedure, the yield, as determined by several experiments, was 73-74% of the theoretical. This, coupled with the comparative ease and economy of the method,

[1] In this paper the pressure was given as 10 mm. Since then the manometer then used has been recalibrated. Corrected pressure: 30 mm. B. P. 210 - 215°.

makes it far superior to that employed in my first paper, which involved two operations, (1) making of the iodo acid from m-iodo benzaldehyde (2) conversion to the ester by absolute alcohol.

However, when I came to attempt the synthesis of benzyl cinnamate by an analogous method, I did not meet with the same success. Benzyl acetate, as shown by Conrad and Hodgkinson (A. 193,300) and more fully by Bacon (Am. 33,94), does not react towards sodium in the same way that the lower aliphatic acetates do, the chief product of the reaction being benzyl alcohol.

In the initial experiments it was found impossible to add sodium wire to an ethereal solution of benzyl acetate, as a vigorous reaction ensued even at 0°. A typical experiment was as follows:

To 100 cc. of anhydrous ether containing 2.3 g. sodium wire was added slowly a mixture of 20 g. benzyl acetate and 10 g. benzaldehyde, the temperature of the whole being kept less than 5°. There was no noticeable reaction until about one third of the mixture had been added, when a white flocculent precipitate became evident, accompanied by evolution of bubbles from the sodium. In spite of good cooling, a gradual rise in temperature set in, until 10° had been reached, when momentarily the reaction went out of control, the temperature passing 20°. The precipitate had become a reddish brown.

After the addition of all the mixture, the product was

treated in the usual way - neutralized with glacial acetic acid, washed with water, separated, and washed with soda solution. The soda wash was acidified, on which a precipitate, half oil, half solid, came down, which solidified on cooling.

After washing the ethereal extract with soda solution and drying with $CaCl_2$, the ether was distilled off, and the residue subjected to vacuum distillation. At 10 mm. the greater portion distilled at 96° C; then the temperature rose indefinitely to over 200°, with comparatively little oil passing over. Obviously, then, there could have been very little benzyl cinnamate present. The low boiling portion was fractionated at atmospheric pressure, with most passing over at 204° (corrected), and possessing the characteristic sweet smell and oily feel of benzyl alcohol.

From the above it is seen that, under the conditions of the experiment, the benzyl acetate, far from condensing to a more complex molecule, had been saponified at some stage to the alcohol.

As time was lacking for side investigations, this reaction was not gone into as fully as it should have been. By varying the conditions (e.g. a more rigorous control of temperature, use of sodium lumps instead of wire, and selection of a different solvent) the desired condensation may possibly be attained.

A point of interest for future work would be the investigation of side products obtained by the above procedure,

such as the acid or acids obtained above from the soda wash, and the higher fractions of the neutral portion. These latter are undoubtedly in part esters, as treatment with KOH yielded acidic and neutral constituents; these interesting points could not, however, be followed up in the time at my disposal.

D. Preparation of derivatives of 2-oxydiphenyl.

Our attention was drawn to o-oxydiphenyl by a description (U. S. Dept. of Agriculture, Clip Sheet No. 778) of its use as a disinfecting agent for destroying tubercle bacilli on premises where tuberculosis is being eradicated. It is described as being most effective without being severely toxic to the animals. (Jour. Franklin Inst., July 1933).

1. Unsuccessful attempt to prepare an iodo derivative of o-oxydiphenyl from p-iodoaniline and phenol.

Hirsch (B. 23, 3705 ff) obtained a mixture of ortho and para isomers of oxydiphenyl, besides a considerable amount of the isomeric diphenyl ether, from the interaction of benzene diazo chloride and phenol. Yields were not stated, nor the method of separating the isomeric oxydiphenyls. Hoping to obtain iodo derivatives by this method, I proceeded as outlined below.

50 g. p-iodoaniline were dissolved in 100 cc. of concentrated HCl (36%) and 200-300 cc. H_2O by heating. The

rapidly cooled mixture was then diazotized with 18 g. $NaNO_2$ to blueing of starch-KI paper. The resulting solution was extracted with successive 100 g. portions of 95% phenol. Five portions were used, but the last two showed only the constant gain in weight due to the water taken up.

This rapidly darkening phenol solution was partly dried with a little solid NaCl, then heated on the water bath in small portions (run in with a dropping funnel) under a reflux. The gas evolution was very sluggish as compared with that observed in the interaction of benzene diazo chloride and phenol. When the reaction was at an end, the product was washed with saturated NaCl solution and distilled. When most of the phenol had come over (some iodine fumes were noticeable) the distillation was continued in a vacuum. The only product other than phenol which distilled was a sluggish black oil which solidified in the condenser and receiver. At 10 mm. pressure most of this came over (with some decomposition, as iodine vapors were still evident) up to 235° C.

The product was worked up for acidic and neutral constituents.

(a) The solution in hot toluene was extracted with hot dilute NaOH solution until nothing precipitated on acidification.

(b) This NaOH extract, green in color when dilute, was extracted with hot toluene after acidification.

On distillation, the toluene solution (b) afforded a black tar, which, when subjected to vacuum distillation,

yielded only phenol, there being practically no high boiling constituents. (a), however, when subjected to the same procedure, gave a pale yellow distillate to 200° C (10 mm.) which solidified in the receiver. On crystallization from alcohol, it formed silvery white plates melting at 128° C. The analysis for iodine proved very unsatisfactory:

Wt. sample	AgI	% iodine
.2425 g.	.3459 g.	77.11 %
.1921	.2742	77.16

The theoretical amount of iodine in $C_6H_4I - O - C_6H_5$ is 42.88%, in $C_6H_4I - O - C_6H_4I$, 60.16%. The above compound may have been formed during distillation by the free iodine vapors observed, which possibly introduced more iodine into the nucleus. However, as the compound was certainly not what we desired (being insoluble in NaOH solution), and as time was short, further investigation was dropped for the time being.

2. Preparation of 5-iodo-2-oxydiphenyl.

The above compound was obtained from 5-amino-2-oxydiphenyl by the usual reactions. The amino compound was prepared from 5-benzeneazo-2-oxydiphenyl obtained according to Borsche and Scholten, B. 50 (1917), 601.

17 g. of o-oxydiphenyl were dissolved in a solution of 15 g. NaOH in 350 cc. H_2O. To this cooled solution was

added gradually, with vigorous stirring, a cold diazo benzene chloride solution from 10 g. aniline. After filtering from the slight precipitate, the solution was decomposed with carbon dioxide. The crude may be crystallized from glacial acetic acid.

(a) Preparation of the amine from the above.

Borsche's method of reduction in aqueous, hot alkaline solution with sodium hyposulphite ($Na_2S_2O_4$) was discarded as being both too laborious, involving the preparation of $Na_2S_2O_4$, and too slow, quite long heating being necessary for complete decolorization. In its place the usual reduction method for similar azo compounds was used, zinc dust and glacial acetic acid on the hot alcoholic solution of the azo compound. This afforded a quick, efficient method of preparation of the amine hydrochloride.

40 g. of the crude benzeneazooxy-diphenyl were dissolved by heating in about 800 cc. of 95% alcohol, and about 20 g. of zinc dust added to the filtered solution. While the mixture was being refluxed, 25 cc. of glacial acetic acid were added slowly through the condenser. After a short time, a heavy white precipitate appeared, which rapidly increased until the material within the flask was almost a solid, somewhat like a stiff jelly. If, after extended heating, the mixture did not become pure white, a small amount more of zinc and acetic acid was added and the whole refluxed again

to decolorization. When this result was obtained, the whole reaction mixture was transferred to a beaker, cooled rapidly (to prevent oxidation and resinification), filtered, and washed with cold alcohol. This removed the aniline by-product. The residue was largely zinc acetate and the amino oxy-diphenyl, and because of their similar solubility curves in alcohol could not be purified from that medium. Extraction with benzene yielded a fairly pure product but was extremely tedious, due to the low solubility of the product in benzene. The method found to give best results was to dissolve the partly dried product in excess hydrochloric acid and crystallize out the hydrochloride, the $ZnCl_2$ remaining in solution. By using a small amount of solvent the yield approaches the theoretical but is quite impure. By using a total volume of about 200 cc. (for the above run) and adjusting the HCl concentration to give a good yield of crystals in a cooled test portion, a yield of 29 g. of well crystallized, only slightly colored needles of melting point 214° - 216° C was obtained. The theoretical yield on the basis of the benzene-azooxy-diphenyl used is about 33 g. If the pure amino compound was desired, the aqueous solution of the hydrochloride so obtained was decomposed with Na_2CO_3 solution, the resultant white precipitate, after being crystallized from alcohol, giving a melting point of 201°C.(corr.) (Borsche gives 201° as the melting point of pure 5-amino-2-oxy-diphenyl).

(b) Diazotization and conversion to the iodo derivative.

In the work done on the preparation of this compound the notes of Neumann (A. 241, 70 - 74) on the preparation of iodo phenols were found of the utmost value.

In the initial attempts diazotization of a solution of the amino compound in an excess of HCl was attempted. This generally resulted in much tar formation. When the solution of KI was added, a yellow precipitate was noted, which on warming to less than 50° C rapidly darkened with some gas evolution. A black spongy tar was formed which continued to evolve gas within itself for some days. After ending this reaction by more heat (to about 80° C), the tar was taken up in NaOH solution, reprecipitated with HCl, and taken up in ether. On vacuum distillation, some clear oil passed over at 190° - 200° C. Another run was distilled with super-heated steam instead of in a vacuum, and yielded an oil which, on conversion to the acetyl derivative, gave a melting point of 82° C (see later).

The second attempts were patterned more closely after Neumann's procedure (A. 241, 70). First 3.1 g. $NaNO_2$ in 50 cc. of H_2O($T < 5^\circ C$), then 7.5 KI in 50 cc. H_2O were added slowly to a solution of 10 g. amino oxydiphenyl hydrochloride in 150 cc. of H_2O($T < 5^\circ C$). A yellow flocculent precipitate of the diazo compound formed. The reaction mixture was then decomposed by the gradual addition of 8.75 g. of the usual concentrated HCl (about 36 - 37%). No tar was formed. A very

slow gas evolution was observed. On standing over night at room temperature, the yellow precipitate turned green and darkened slowly with gradual gas evolution, hastened by mild warming. From 35° to 50° the solid gradually changed to a black, tumescent tar, which continued to evolve gas within itself for some time. After dissolving the tar in dilute NaOH solution containing some sulphite, it was precipitated with dilute HCl and extracted with $CHCl_3$. By vacuum distillation, 5 g. of a product boiling at 200° - 205° (10 mm.) were obtained, somewhat discolored with iodine. By uniting the yields from several runs and redistilling, a fairly light colored oil was obtained which did not solidify on long standing at low temperatures.

Because of this supercooling characteristic of the product, it was converted to the acetyl derivative as follows: 7 g. of the oil were refluxed 2 hours with 20 g. acetic anhydride and 2 g. sodium acetate. After cooling, the product was taken up in ether and washed alternately with cold H_2O and 5% NaOH solution until the wash water showed an alkaline reaction. After washing once more with water the solution was evaporated on the water bath. The resultant oil, on standing in the ice chest, crystallized from several centres. Crystallization may be hastened by the use of seed crystals. The yield was 7 g. By crystallizing twice from ligroin (B.P. 90° - 105°), white crystals of M.P. 82° C (corr.) were obtained, which gave the following results when analyzed for iodine by the

method of Carius:

Wt. sample	Wt. AgI	Percent iodine
.1532 g.	.1068 g.	37.68%
.2358	.1646	37.73

The value calculated for $C_6H_5C_6H_3IOCOCH_3$ is 37.57% iodine.

As a final test of the identity of the substance with that obtained by Mr. Niven by an entirely different procedure, the melting point of a mixture of the two was taken. It proved unaltered, i.e., 82° C.

In an effort to improve the yield, the dry diazo chloride was isolated as below; I am indebted to Neumann (ibid.) for a description of the method as applied to iodophenols.

20 g. of crude amino hydrochloride were dissolved in a little absolute alcohol, cooled with ice water, and 10 g. of ethyl nitrite were allowed to evaporate into the solution. A heavy precipitate formed when the reaction was well under way. When all the nitrite had passed over, much anhydrous ether was added. The filtered product, washed with ether, formed a pale grey-green powder of melting point about 107 C. with decomposition. A yield of 20 g. was obtained, the theoretical being 21 g.

The above obtained 20 g. of diazo chloride were added to about 150 cc. of cold water. Little solution ensued. From a burette 33 cc. of hydriodic acid (containing $\frac{11}{4000}$ equivalents per cc.) were added. No reaction was noticed until

the mixture was warmed, when the reaction ran exactly the same course as when the diazo chloride was not first isolated. A better yield was obtained, however, there being 18 g. of tar extracted.

3. Preparation of sodium orthophenylphenate.

In preparing this salt in the dry state, the procedure given in Beilstein's Handbuch for the preparation of sodium phenolate was followed.

One mol of sodium was dissolved in absolute alcohol and added to a solution of one mol o-oxydiphenyl in absolute alcohol. The reaction mixture was evaporated in a stream of hydrogen, and the crude product crystallized from acetone. The crystals so formed could not be dried by warming, as they charred in a very short time, even at 50° C. in an evacuated desiccator.

Dried at room temperature in a vacuum, the product was analyzed by titration of the aqueous solution with standard HCl, using phenolphthalein as indicator. Values obtained follow:

Wt. sample	Vol. HCl(.1123 n.)	Percent Na
.5993 g.	21.4 cc.	9.22 %
.5992	21.3	9.18

The calculated value for $C_6H_5C_6H_4ONa$ is 11.98% for $C_6H_5C_6H_4ONa\cdot(CH_3)_2CO$, 9.20%. Hence the product is obviously the sodium salt crystallized with one molecule of acetone.

Synopsis of Results.

1. Preparation of benzyl cinnamate from benzyl alcohol and cinnamoyl chloride (method not given in literature).

2. Preparation of the new compound m-iodo-cinnamoyl chloride-properties, analysis.

3. A corrected melting point for m-iodo cinnamic acid (191.5° C. instead of 181° C. with decomposition as given by Gabriel, Herzberg, B. 16, 2037).

4. Preparation of the new compound benzyl m-iodo cinnamate-properties, analysis.

5. Preparation of m-iodo benzyl alcohol from m-iodo benzaldehyde (method not applied before).

6. Preparation of the new compound m-iodo benzyl cinnamate-properties, analysis.

7. Preparation of ethyl m-iodo cinnamate (see previous paper for bachelor's degree, 1932) by condensation of m-iodo benzaldehyde with ethyl acetate by means of sodium; subsequent saponification of the ester to the acid.

8. Preparation of 5-amino-2-oxydiphenyl by reduction of the benzeneazo compound with zinc and acetic acid (method not given in literature).

9. Preparation of the new compound 5-iodo-2-oxydiphenyl - properties .

10. Preparation from the above of the new compound 5-iodo-2-acetoxydiphenyl - properties, analysis, identification with

the product obtained by Mr. Niven (thesis for bachelor's degree, 1934).

11. Preparation of the new compound $C_6H_5C_6H_4ONa \cdot (CH_3)_2CO$. Analysis.

Some negative results were obtained, such as the reaction between benzyl acetate and benzaldehyde induced by sodium, and the reaction between phenol and p-iodo benzene diazo chloride. These reactions, while not giving the desired compounds, yielded products which it was not possible to investigate further, on account of lack of time.

Note: All journal references are abbreviated as in Beilstein's "Handbuch"; e.g., B. signifies "Berichte der deutschen chemischen Gesellschaft."